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PROCEEDINGS OF THE TUMOUR BOARD OF THE AGHIA SOPHIA CHILDREN'S HOSPITAL TUMOUR STUDY GROUP, ATHENS, GREECE

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Neuroblastoma Metastatic to Brain

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F. Tzortzatou-Stathopoulou, MD, PhD (Associate Professor of Pediatric Oncology)

The patient to be discussed today has a most unusual manifestation of neuroblastoma, namely, a brain metastasis. Clinical management was therefore difficult, and led to many discussions during her clinical course. We shall review those discussions in the Tumor Board, and present the outcome of the treatment she received.

A. Xaidara, MD (Pediatric Oncology Registrar)

The patient is a 2-year-old girl who had an uneventful medical history until she developed proptosis and periorbital ecchymosis of the left eye. The clinical picture suggested metastatic neuroblastoma (NBL) and work-up included ultrasound (US) and computed tomography (CT) scans. These showed a huge mass arising in the left adrenal medulla, crossing the midline and displacing the left kidney downward. A ^{123}I-MIBG examination showed increased uptake in the abdomen at the site of the mass as well as multiple bone deposits. The urine VMA was normal as were other laboratory studies except for mild anaemia. Bone marrow aspiration and biopsy showed marrow infiltration with rosettes.

The tumor was unresectable and the child received chemotherapy with vincristine, cisplatin, cyclophosphamide, doxorubicin, etoposide, and teniposide. The response to treatment was good, and after five courses of chemotherapy the patient underwent a complete excision of the residual primary mass.

Histologic examination confirmed the diagnosis of ganglioneuroblastoma [1] (Fig. 1). The child received a total of 14 courses of chemotherapy, when evaluation by CT, US, MIBG, and bone marrow examinations showed her to be in complete remission.

The patient remained off therapy and in very good health until 18 months from diagnosis. She then presented with headache, vomiting, and truncal ataxia. A CT showed a brain tumour but her previous neuroblastoma lesions continued in complete remission.

A ^{123}I-MIBG examination showed uptake in the brain tumor, but no other sites were identified. May we now review the imaging studies obtained at this point, Dr. Hadjigeorgi, please?

Ch. Hadjigeorgi, MD (Pediatric Radiologist)

The brain CT at the time of the first admission showed only the metastatic lesions outside of the brain; that is, the bony wall of the orbit with the accompanying proptosis. The initial abdominal CT with intravenous contrast enhancement showed an obvious tumor mass with necrosis and calcification located along the left retroperitoneal space, crossing the midline and extending to the right. The ^{123}I-MIBG scan also displayed uptake in the primary tumor (Fig. 2). Metastases were present in the skull, limbs, ribs, and long bones. As we have heard, these signs disappeared with treatment and there was no evidence of residual disease.

The contrast-enhanced CT of the brain at the time of the second admission because of headache and ataxia revealed a tumor of the cerebellar hemisphere ($4 \times 4.5 \times 6$ cm) with surrounding edema (Fig. 3). There was at least one area of calcification within the mass. At that time, chest X-ray films, abdominal ultrasound, bone scan, and CT scans of the chest, abdomen,

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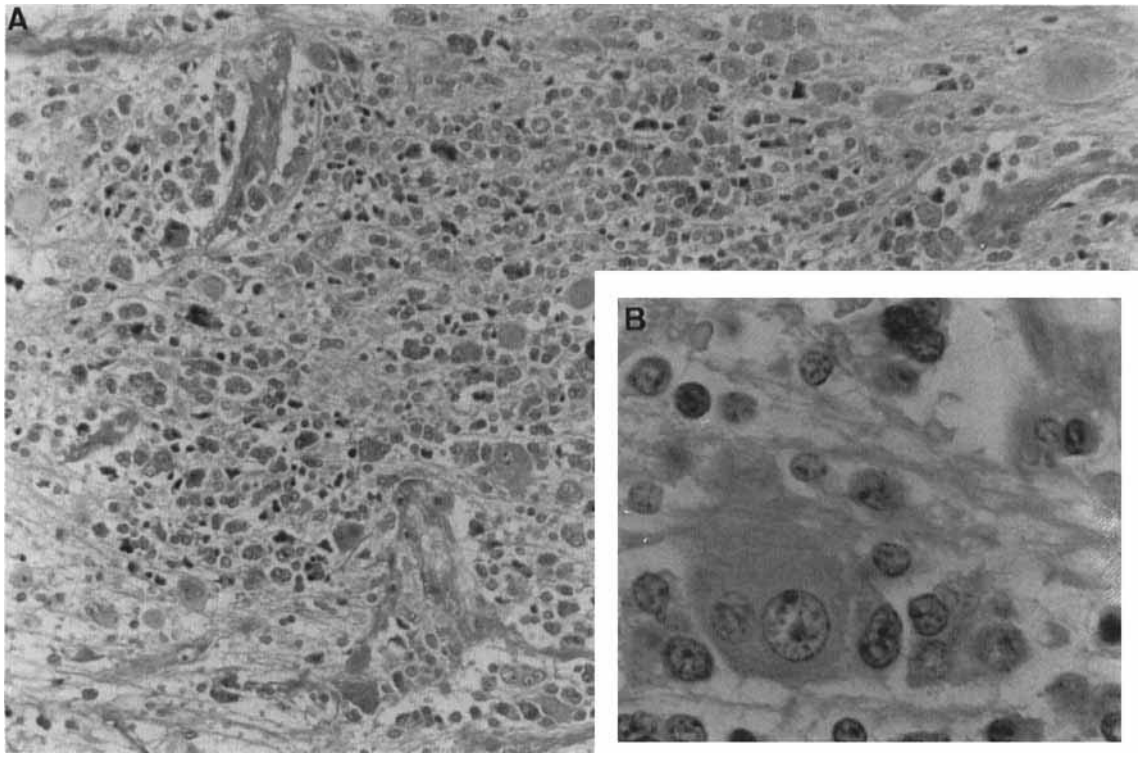

Fig. 1. Adrenal ganglioneuroblastoma. Appearance after chemotherapy. **A:** H&E, ×25; **B:** Detail, ×400.

and pelvis were all negative, and the ^{123}I-MIBG scan was positive only at the site of the brain tumor (Fig. 4).

M. Andrioti, MD (Pediatric Oncology Resident)

Is this brain lesion a separate primary or a metastasis?

Dr. Tzortzatou-Stathopoulou. That is the differential diagnosis of course. This particular location would be very unusual for a neuroblastoma metastatic lesion, although intracranial deposits have been described [2].

Management is extremely difficult in either case. The outlook for children with Stage IV neuroblastoma is very poor under any circumstances, and the presence of a brain lesion is doubly disturbing. Should surgery be performed now? Her signs are impressive. Would removal of the tumor, or at least a "debulking" operation improve the chances for survival? Would such an operation establish the nature of the brain tumor; i.e., whether metastatic or primary and thus help us define how aggressively she should be treated?

N. Prodromou, MD (Pediatric Neurosurgeon)

The child is symptomatic. Total removal is possible, which would really relieve the patient's immediate problems.

Dr. Tzortzatou-Stathopoulou. This approach is attractive since the primary tumor is in remission. Total removal of the brain lesion followed by radiotherapy and chemotherapy might increase her chances for longer relapse-free survival.

One always strives for cure, but we must face the realities in this case. She has only a small chance of cure for the one site and perhaps a similarly small chance for cure with the other, if it proves to be a separate brain tumor.

V. Mikraki, MD (Pediatric Oncology Registrar)

Is a trial of chemotherapy worth considering? We could see whether the brain tumor responds and then proceed accordingly.

Dr. Prodromou. We do not have the luxury of time. The patient is symptomatic now, with cerebellar signs as well as intracranial hypertension. Immediate action is indicated. Rapid increase in size of these masses, most of the time because of bleeding, can lead to coma and even to death. It would be safer at least to decompress the posterior fossa prior to any treatment. I believe it would be preferable to remove the mass as soon as possible, since it seems eminently operable.

Dr. Tzortzatou-Stathopoulou. All treatment options at this point have their associated risks. I therefore believe strongly that the family must help us reach a deci-

Fig. 2. MIBG uptake in the primary adrenal tumor (arrows).

sion, after full explanation of the clinical problems confronting us.

INTERVAL NOTE

The parents agreed with the decision to proceed with surgery and removal of the brain tumor to relieve the intracranial pressure and to confirm the diagnosis. Accordingly, preoperative dexamethasone was started and the patient was taken to the operating room.

Dr. Prodromou. A ventricular catheter was inserted into the right ventricle and a small quantity of CSF was removed. A traditional posterior fossa exploration was performed. After the dura was incised, a brownish tumor was identified underneath the mid-third of the right cerebellar hemisphere, which was infiltrated by the lesion. A cyst-like formation within the tumor obviously was the result of a previous hemorrhage. The tumor had a terribly rich blood supply, but the bleeding stopped after total tumor removal. The venous drainage was mainly through a large cortical vein in the lower aspect of the cerebellar cortex. It drained directly into a dural venous lake which communicated with the torcular Herophili. Meticulous hemostasis was achieved and the wound was closed in the traditional way.

Dr. Tzortzatou-Stathopoulou. Do your findings help us in deciding whether this tumor is primary or metastatic?

Dr. Prodromou. The pattern of venous drainage was typical of a metastasis rather than a primary growth.

What was the histopathological appearance, please, Dr. Arvanitis?

D. Arvanitis, MD (Consultant Pathologist)

The brain tumor has the histological picture typical of a stroma poor, undifferentiated neuroblastoma according to the criteria of Shimada et al. [1] (Fig. 5). Its appearance is similar to the neuroblastic component of the stroma-rich intermixed type ganglioneuroblastoma that was found in the left adrenal a year ago (Fig. 1). The question whether this represents a second primary or a metastasis cannot be answered histopathologically. The possibility of a second primary is very remote, however, because primary neuroblastomas of the cerebellum are extremely rare.

Dr. Tzortzatou-Stathopoulou. Dr. Grafacos, do you think that heavy therapy and autologous bone marrow "rescue" is an option in this case?

S. Grafacos, MD (Bone Marrow Transplantation Unit)

No, I don't think so, because she now has only brain involvement that therefore calls for local, intensive therapy. It is, of course, possible if not probable there are persisting metastatic foci elsewhere. There are too many uncertainties to warrant the rigorous treatments and morbidity inherent in bone marrow transplantation. In summary, she is not now a good candidate in my opinion.

INTERVAL NOTE

It was decided to give three courses of cisplatin plus etoposide chemotherapy and then irradiate the brain but not the spinal cord because the CSF was normal. Further chemotherapy would then be continued.

Dr. Xaidara. The child received 24 Gy whole brain irradiation with a supplement to the tumor bed, bringing the total there to 40 Gy. Afterwards, chemotherapy was resumed, but ^{123}I-MIBG follow-up examination while on chemotherapy showed relapsed neuroblastoma in multiple bony sites, though not in the brain (Fig. 6).

DISCUSSION

Dr. Tzortzatou-Stathopoulou. The appearance of brain metastases in any cancer patient has generally heralded a poor prognosis, like in this child. Questions remain regarding this very unusual clinical manifestation of neuroblastoma. They include:

Fig. 3. Two views of CT scan of the brain. There is a large calcifying tumor within the right cerebellar hemisphere with surrounding edema.

1. How long was this tumor present in the cerebellum? At diagnosis, the CT was negative for brain involvement and the MIBG scan 6 months ago was also negative.

2. Dissemination of the disease originally was in bones without any soft tissue masses. Could the skeletal metastases act like primary tumors and lead to metastases at other sites? This is always a question for which there is no ready answer. Another of our neuroblastoma patients makes one speculate along those lines. The child had several metastases that cleared except for only one that persisted in the femur. All the several other lesions seemed to be under control. The patient subsequently developed bilateral pulmonary metastases. The lungs, like the brain, are not often affected by neuroblastoma. I am tempted to think that the femoral lesion was different phenotypically from the rest of the disease and behaved in an aberrant way, both in resisting therapy and perhaps in shedding daughter cells that produced metastasis in an exceptional site.

There certainly are indications that specific metastases in patients with disseminated disease may not take up MIBG, while other deposits in the same patient do so [3]. Such a difference in the metabolic profile might be correlated with a different clinical "aggressiveness." Such an hypothesis could fit the patient with the femoral lesion just described.

3. Finally, the extraordinary case reported by Shah et al. needs to be mentioned [4]. That child, unlike ours, seems to have had a separate, primary posterior fossa tumor as part of the expanded concept of the IV-S syndrome and

Fig. 4. MIBG scan, lateral view, showing pronounced uptake in brain tumor (arrow).

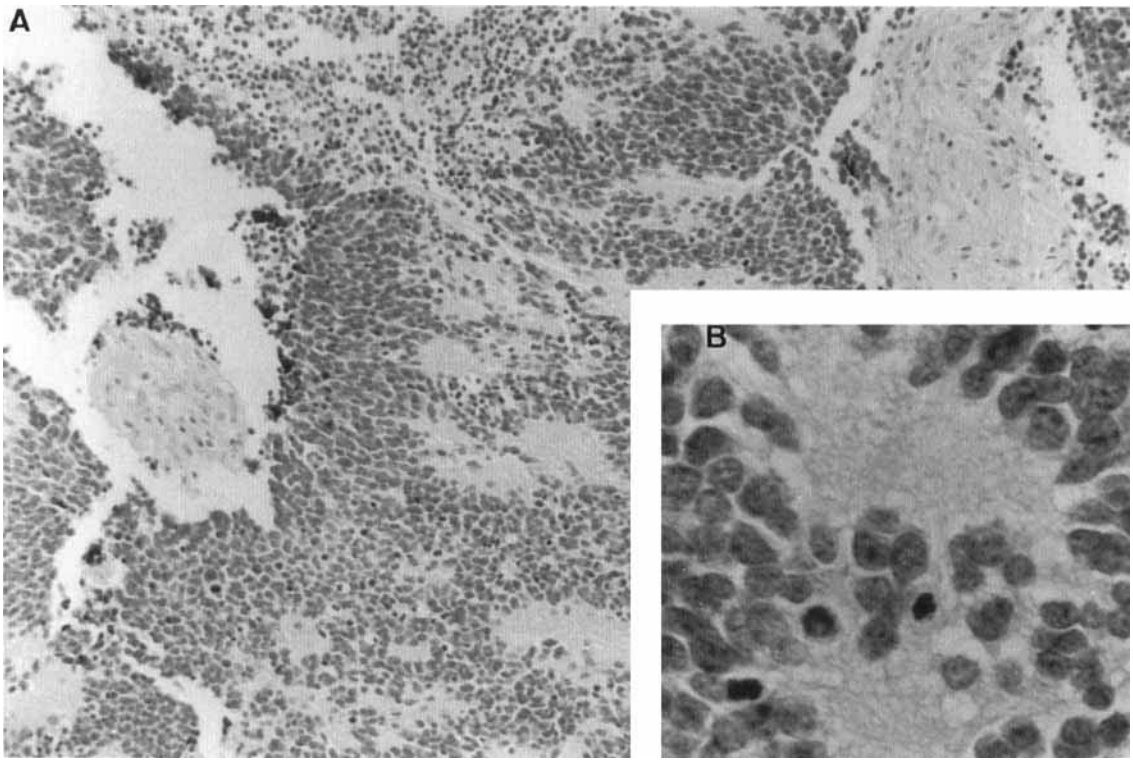

Fig. 5. Cerebellar neuroblastoma. **A:** H&E, ×25; **B:** Detail, ×400.

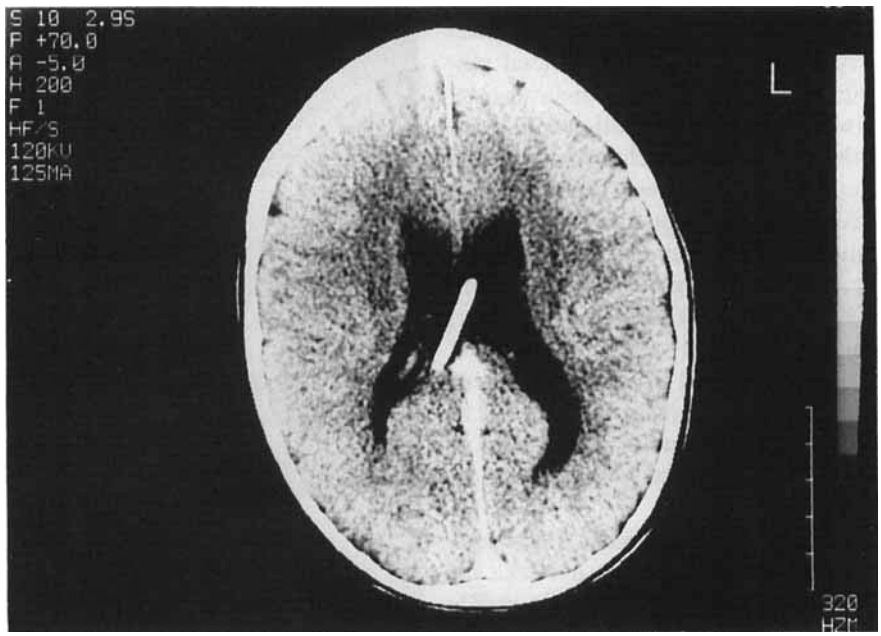

Fig. 6. CT scan of the brain when the patient had relapsed in the skeleton. There is no cerebellar mass visible.

not a metastasis [5]. Their patient, again unlike ours, fared well and is a long-term survivor. Both children had cerebellar lesions. The contrast in their outcomes underlines the prognostic importance associated with the patterns of disease at diagnosis, the one compatible with low-risk neuroblastoma, and ours unfortunately with high-risk disease.

In summary, our patient with neuroblastoma had a most unusual clinical course. First, she developed a posterior fossa metastasis, a very unusual site. Second, the CNS lesion became evident at a time her multiple other secondary deposits in bone were in complete remission. Third, the cerebellar lesion was treated like a second independent, primary lesion and remained under control even while her other metastases recurred.

Neuroblastoma remains an enigmatic and frustrating process.

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SERIES EDITOR'S NOTE

This Proceedings from Athens need not be a stimulus (Latin = *goad;* old English = *spear*) for recalling a few of the countless words in Medicine[1] and Science[2] that stem from the Greek. Rather we can turn to other sources.

The names of acute observers become attached to anatomic parts, diseases, and syndromes, giving rise to the myriad[3] eponymic[4] terms in the vocabulary.[5] The French have made many such eponymic contributions not only to specialty language but also to everyday speech. Some of these terms are well known, some not. *Pasteurization* is a household word, of course, named for the great Louis Pasteur (1822–1895). Another Louis, *Braille* (1809–1852) who was a contemporary of Pasteur, invented the system of raised dots that enables the blind to read and write. He himself had been blind since the age of three and devoted his life to teaching those similarly handicapped.[6]

Less known are the French diplomats remembered in botanical names that are used daily. Jean Nicot was a 16th century ambassador to Lisbon. He obtained samples of the New World tobacco plant, whereon all plants of this genus were named after him (*nicotiana*), as was the alkaloid *nicotine* derived therefrom. [*Tobacco* is derived from the Caribe[7] Indian word for the tube (pipe) used in smoking tobacco, or for a roll of leaves of the plant to form a rough and ready cigar, and smoked as such.] Another French diplomat, Michel Begon (1638–1712), the governor of Santo Domingo is remembered in *begonia. Magnolia,* however, is named after the botanist Pierre Magnol (1638–1715) and *bougainvillea,* the beautiful tropical[8] vine, after still another Louis, Louis Antoine de Bougainville (1729–1811). He was a noted French navigator, explorer and soldier. His explorations of the South Pacific rival those of his better known English contemporary James Cook (1728–1779). De Bougainville also served under General Montcalm in Canada and fought the British in Martinique when France sided with the colonists in the American Revolution.

A less happy association is that with Joseph-Ignace Guillotin (1738–1814). Dr. Guillotin was a highly respected member of the French medical establishment. Among several of his notable contributions to the public was his service on the commission to investigate Mesmerism. It is interesting to note that the commission included Benjamin Franklin, then the American agent assigned to France. [They found that Mesmer[9] was a charlatan (Italian: *ciarlare* = a verb applied to the patter of vendors promoting drugs.)] Guillotin served with de la Rochefoucauld on the Poverty Committee that concluded that the state owed "prompt, free, assured and total (medical) care" to the needy—and this 200 years ago! It was as part of his drive for egalitarianism (Latin: *equalis* = equal) that he made his proposal regarding the execution of prisoners. He advocated that the means should be the same regardless of the social standing of the person receiving the death sentence. In those days, nobles were beheaded with a sword, an "honorable" weapon, and died quickly without pain. By contrast, commoners were dispatched ignominiously (Latin: *ig* + *nomen* = without repute) often by unspeakably cruel methods. His proposal went on to state that the

[1]Latin: *medicus* = physician.
[2]Latin: *sciens* = having knowledge.
[3]Greek: *myroi* = countless, ten thousand.
[4]Greek: *epi* = after + *onoma* = name.
[5]Latin: *vocabularius* = verbal.
[6]English: *hand-in-cap* = an old English system of barter and quasi-gambling game.
[7]*Caribe* from the Arawak *carib* = strong or brave men.
[8]Greek: *tropikos* = turning, here of the sun at the solstice (Latin: *sol* = sun + *sistere* = stand still) half-way between the *equinoxes* (Latin: *equus* + *noctis* = "equal nights" when the hours of daylight and dark are equal. The solstices are when the sun appears to "stand still" at a point in the heavens having reached its farthest point from the equator.
[9]Franz Anton Mesmer (1734–1815) was a Viennese physician. He developed the discredited theory of "animal magnetism," from which, however, stemmed hypnosis (from *Hypnos,* the Greek god of sleep).

means should be beheading "by a simple mechanism." Though the "simple mechanism" itself was developed and perfected by others, his fame and his public espousal of the machine linked his name with the instrument—the guillotine—and to the technique, both of which carry his name forward to this day. It is a minor tragedy [Greek: *tragos* = goat + *aide* = song (of uncertain meaning)] that he is so remembered rather than for the several enlightened, humanitarian activities that would do better justice to his life and work.[10] It would seem that Dr. Guillotin has become the goat in this affair.

[10]Weiner DB: The real Doctor Guillotin. JAMA 220:85–89, 1972.